**Aims:** (a) To investigate the HPSE expression in chronic liver injury and (b) to study its effects on the fibrosis process.

**Materials and methods:** 1. **Experimental design:** CCL4 model for fibrosis was utilized in 20 BALB/cj mice. 2. **In vitro studies:** HPSE expression was assayed by treatment of macrophages (RAW 264.7 cell line) by real time RT-PCR and western blot analyses. Furthermore, we evaluated the HPSE activation of HSCs (LX-2 cell line). Finally, the migration of macrophages (RAW 264.7 cell line) was assayed by treatment with HPSE.

**Results:** HPSE expression in liver tissue of CCL4-treated mice increased after 1 and 2 weeks of treatment but not after 8 and 12 weeks. Immunostaining analyses revealed that HPSE was restricted in the centrilobular areas with both necro-inflammatory damage and fibrosis, and co-localized with macrophage markers F4/80 and CD68. TNF-α treatment of U937 macrophages significantly increased HPSE mRNA and protein expression, as well as HPSE secretion. Using the conditioned medium of TNF-α-pre-treated U937, we found that macrophage-secreted HPSE regulated the expression of both α-SMA and fibronectin in LX-2 cells. Finally, macrophages with latent HPSE significantly increased the cell migration rate.

**Conclusions:** Overall, HPSE is involved in early stages of fibrosis process. Inflammatory macrophages could be an important source of HPSE. In this context, HPSE may play a role in the macrophage-mediated activation of HSCs and in migration of macrophages themselves.

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**T-05**

**Local renin–angiotensin system in the kidney of ascitic cirrhosis: An innocent bystander or a major protagonist?**

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**Introduction:** In liver cirrhosis, kidney local renin–angiotensin system (RAS) deserves scrutiny and includes: conversion of angiotensin I into angiotensin II (Ang-II) by ACE and chymase; binding of renin and prorenin to their tissue receptor (RPRr), and hence local generation of angiotensin I and Ang-II; conversion of Ang-II by ACE2 into angiotensin1-7; degradation of the latter to angiotensin1-4 by nepriylisin. Changes in expression of these enzymes and receptors affect renal levels of sodium-retentive (Ang-II) and natriuretic (angiotensin1-7) peptides.

**Aims:** To assess, in ascitic rats’ kidney, expression and immunolocational of major components of RAS and their hormonal consequences.

**Methods:** Healthy rats (group G1) and rats with ascitic cirrhosis (group G2) were studied. Kidney content of ACE, chymase, RPRr, ACE2, nepriylisin, Ang-II, angiotensin1-7 and plasma levels of Ang-II, direct renin (DR), plasma renin activity (PRA) were measured. DR is quantified through monoclonal antibodies that bind both active renin and prorenin, and therefore plasma concentrations of prorenin can be derived from the ratio DR/PRA.

**Results:** DR/PRA ratios were 3.3 ± 0.8 and 7.9 ± 1.6 in healthy and ascitic rats, respectively (P<0.03), showing more prorenin in ascitic rats. In G2, Ang-II was higher than normal in plasma (P<0.01) but especially in renal tissue (1150 ± 199 vs. 78 ± 22 pg/mg kidney protein, P<0.001). Kidney content of ACE, chymase, ACE2 and nepriylisin was significantly higher, but RPRr significantly lower, in ascitic than in healthy rats. The ratio Ang-II/Angiotensin1-7 in kidneys rose from 1.3 ± 0.2 in G1 to 5.3 ± 0.4 in G2 (P<0.03).

**Conclusions:** In ascitic cirrhosis: (a) the contribution of ACE and chymase to renal Ang-II synthesis seems stronger than that of RPRr, despite increased plasma prorenin; (b) the kidney shows an imbalance in favour of the production of anti-natriuretic Ang-II because overexpressed nepriylisin finally degrades ACE2-generated angiotensin1-7.

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**T-06**

**Durable response in the markers of cholestasis through 24 months of open-label extension with obeticholic acid in Italian patients with primary biliary cholangitis**

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**Introduction and aim:** Obeticholic acid (OCA) is a potent and selective farnesoid X receptor (FXR) agonist under investigation for the treatment of primary biliary cholangitis (PBC). This analysis evaluated the long-term efficacy and safety of OCA in Italian patients with PBC.

**Material and methods:** POISE was a Phase 3, 12-month, double-blind, placebo-controlled study followed by an ongoing open-label extension (OLE). Patients with an alkaline phosphatase (ALP) >1.67x ULN and/or bilirubin >ULN to <2x ULN, on a stable ursoeodeoxycholic acid (UDCA) dose or inability to tolerate UDCA, were randomized to daily Placebo, OCA 5–10 mg, or OCA 10 mg.

**Results:** Thirty-two of 216 patients were treated at Italian sites (Placebo: n=11; OCA 5–10 mg, n=11; OCA 10 mg, n=10). In Italian patients, both OCA groups demonstrated significant reductions in ALP (ULN) after 12 months of double-blind treatment (Placebo: 43 ± 108; OCA 5–10 mg: −114 ± 86, p<0.01; OCA 10 mg: −132 ± 104, p<0.01). This response was durable through an additional 24 months of treatment during the OLE (Placebo: −105 ± 86, p<0.05; OCA 5–10 mg: −140 ± 78, p<0.01; OCA 10 mg: −122 ± 110, p<0.05). After 12 months of double-blind treatment, total bilirubin (µmol/L) increased in the Placebo group (2.1 ± 2.5), but remained stable in OCA 5–10 mg and OCA 10 mg groups (−0.6 ± 3.5, p<0.05 and −1.1 ± 1.9, p<0.05). The change from Baseline in total bilirubin at month 24 of the OLE remained relatively stable (Placebo: 1.1 ± 5.4; OCA 5–10 mg: −0.3 ± 4.5; OCA 10 mg: 0.4 ± 5.7). Five (45%) of the Placebo patients in the double-blind phase and 8 (80%) of the Placebo patients initiating OCA in the OLE experienced pruritus.

**Conclusions:** OCA given to Italian patients resulted in significant improvements in markers of cholestasis and hepatic damage. A durable response was evident throughout the OLE demonstrating the safety and efficacy of long-term OCA treatment.

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